Published in final edited form as:
Cancer. 2012 June 1; 118(11): 2796–2803. doi:10.1002/cncr.26519.

Young Women with Family History of Breast Cancer and their Risk Factors for Benign Breast Disease

Catherine S. Berkey, ScD[1], **Rulla M. Tamimi, ScD**[1], **Bernard Rosner, PhD**[1], **A. Lindsay Frazier, MD, ScM**[1,3,*], and **Graham A. Colditz, MD, DrPH**[2,*]

[1]Channing Laboratory, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School

[2]Alvin J. Siteman Cancer Center, Washington University School of Medicine

[3]Department of Pediatric Oncology, Dana-Farber Cancer Institute

Abstract

BACKGROUND—Breast cancer (BC) patients wonder how their daughters might reduce their risk. We investigate childhood/adolescent risk factors for benign breast disease (BBD), a well documented risk factor for BC, among girls with a family history.

METHODS—The Growing Up Today Study (GUTS) includes females, aged 9–15yrs in 1996, who completed annual questionnaires 1996–2001, then 2003, 2005, 2007. Participants provided information regarding alcohol, menarche, height, and body mass index (BMI, kg/m^2). Peak height growth velocity (PHV, inches/yr) was estimated from longitudinal heights. On 2005–2007 surveys, 6888 females (18–27yrs) reported whether they were diagnosed with biopsy-confirmed BBD (n=67 cases); 6741 girls (non-cases) reported no BBD. Participants' mothers reported their own biopsy-confirmed BBD and BC, and BC in their sisters and mothers. Stratified by family history, logistic models investigated BBD risk factors.

RESULTS—Young women whose mothers or aunts had BC were more likely to be diagnosed with BBD (OR=2.34, p=.01), as were those with maternal BBD (OR=1.59, p=.095). Adolescents with BC family history (mother, aunt, grandmother) who consumed alcohol (7drinks/week) doubled their BBD risk (OR=2.28, p=.01), similar to those with maternal BBD (OR=1.96, p=.02). Girls whose mother or aunt had BC saw their BBD risk elevated with higher PHV (OR=1.82/(inch/yr), p=.05). Among girls with no family history, BBD risk appeared related to other factors: childhood BMI, adolescent waist circumference, and adult height.

CONCLUSION—Adolescents with family history may reduce their risk by avoiding alcohol. Separate risk factors were observed among girls with family history versus girls with no family history, possibly reflecting different causes of breast cancer.

Keywords

adolescents; pre-teens; family history; alcohol; height; weight; BMI; waist circumference; height growth spurt; peak height growth velocity; age at menarche; BBD; breast cancer; prospective; longitudinal

Corresponding Author: Dr. Catherine S. Berkey, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115. Phone: 617-525-0845. FAX: 617-525-2008. Catherine.Berkey@channing.harvard.edu.
*Co-senior authors

Conflict of Interest: The authors have no conflicts, including financial, to disclose.

INTRODUCTION

When family history is a strong risk factor, such as for breast cancer (1–3), advice to patients' family members on lifestyle factors, that may further influence their own risk, is critically important (4). For breast cancer this advice is timely for adolescent girls, because the genetic influence is particularly strong at younger ages (5); if a woman is diagnosed before age 40yr, her daughter's risk of breast cancer is doubled (6).

Certain factors may provide different levels of risk among women with a family history compared to those without a family history (7). In the Nurses' Health Study, for women with a family history of breast cancer, later age at menarche provided little protection against breast cancer, and no reduction in risk was observed with multiple births or with early age at first birth (7). But in both women with and without a family history of breast cancer (BC), there was increased BC risk associated with their own benign breast disease (BBD) (7). In an older Swedish cohort (women aged 50–74yr), BBD and height were related to increased breast cancer risk in subjects without a family history, whereas not in women with a family history (1). A study of younger breast cancer patients (under 50yr), where each control was a patient's own twin sister, found that childhood height and weight were associated with breast cancer risk only among those without a family history (8).

Benign breast disease is a well established risk factor for breast cancer (9). Among women with BBD, a family history of BC further increases breast cancer risk (10). And women with a family history of BC are more likely to be diagnosed with BBD, especially at younger ages (25–29yrs) (11). BBD may itself have a heritable component, with deficient DNA repair genes exerting influence prior to BBD; the association between BBD and variant alleles in DNA repair genes was significantly stronger among women with a family history of breast cancer (12).

The investigation of childhood/adolescent factors and BBD among young women with a family history may provide insight into the etiology of breast cancer or BBD while providing possible avenues for prevention in those already at higher risk. We recently reported a strong association between adolescent consumption of alcoholic beverages and risk of BBD (13); alcohol consumption by adult women is one of few modifiable factors known to increase breast cancer risk (14–16). We also previously reported higher risk for BBD, likely translating into elevated breast cancer risk, among thinner girls, among girls with the most rapid height growth, and among taller young women (17); these factors were earlier found to be related to breast cancer risk (18–20). Here we use data from a prospective cohort of children, recruited when they were 9–15 years of age, to investigate whether several childhood and adolescent factors are associated with BBD risk in young women with a family history of disease.

MATERIALS AND METHODS

Study Population

Established in 1996, the Growing Up Today Study (GUTS; founding PI: G. Colditz) includes 9037 girls from all 50 states who are daughters of Nurses' Health Study II (NHSII) participants (21). The study, approved by Institutional Review Boards at Harvard School of Public Health and Brigham and Women's Hospital, is described elsewhere (22). Mothers provided informed consent, and their daughters assented by completing baseline questionnaires. The cohort returned follow-up questionnaires annually (on paper or online) from 1996 through 2001, followed by surveys in 2003, 2005 and 2007. The girls' response rate to one or more follow-ups after baseline was 97%. A total of 6927 females (77% of cohort) returned the 2005 and/or 2007 (up to January 1, 2009) surveys inquiring about BBD,

when follow-up ages were between 18 and 27yr. Of these 6927 females, 6905 responded to the BBD question. From them, we excluded 6 girls because their mothers reported they had been diagnosed with childhood cancer, and another 11 girls whose mothers reported them as adopted; no BBD cases were among these 17 exclusions. This leaves us with a total of 6888 females providing BBD information to these analyses.

Benign Breast Disease

The 2005 and 2007 surveys asked "Has a health care provider ever diagnosed you as having Benign Breast Disease?" and, if yes, whether the diagnosis of BBD had been "Confirmed by breast biopsy". Those 6741 females who responded that they had never been diagnosed with BBD provide the non-cases for these analyses. The remaining 147 females reported that they had been given a diagnosis of BBD, though not all were confirmed by biopsy. Among these possible cases are 67 females who reported that their BBD diagnoses were confirmed by breast biopsy, including 27 with biopsy-confirmed BBD reported in both 2005 and 2007, another 29 with confirmed BBD only in 2007 (some returned no 2005 survey), and 11 with confirmed BBD reported in 2005 (but no 2007 survey). These 67 cases and 6741 non-cases provided the data for analyses of biopsy-confirmed BBD. (The remaining 80 females (=147 – 67) who provided less reliable disease reports were excluded entirely from this work.)

Our questionnaires did not ask for date of diagnosis. Most BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass (which was then biopsied), since participants were too young to be undergoing routine screening mammography. A validation study conducted in a large cohort of women, some of whom are mothers of our participants, confirmed the accuracy of women's self-reports of BBD (23). The most common type of BBD occurring in adolescents and young women (the age group we are studying) are fibroadenomas, which account for nearly 70% of benign lesions (24). The remainder are primarily cysts and fibrocystic changes (24).

Risk Factors from Older Childhood and Adolescence

Alcoholic Beverage Intake—Cumulative alcohol intake (servings/week of beer, wine, and liquor) was derived from alcohol consumption variables reported on our 2000, 2001 and 2003 surveys; details regarding its derivation were described earlier (13). A review article on the validity of adolescent self-reports of risky behaviors concludes that the privacy of self-administered questionnaires (such as ours) produces higher, supposedly more valid, reported rates of alcohol use (25).

Height, Weight, and Adiposity—Children reported their heights and weights on every survey, and relative weight status was represented by body mass index (BMI= weight/height^2, (kg/m^2)). Young adult BMI and height were assessed from the 2005 and 2007 surveys, when participants were between ages 18 and 27yr. Further details regarding each of these factors and their validity were provided earlier (17). We also computed change in BMI for each girl, from childhood to young adulthood. The participants, as part of the year 2000 survey when they were 13–19yrs of age, reported their adolescent waist circumference in inches, using a tape measure included with the survey mailing.

Peak Height Growth Velocity (PHV)—Earlier studies of peak growth velocity and its dietary correlates (26, 27) were conducted due to the belief that PHV may be related to adult diseases. From the serial heights on a girl, we computed a series of annualized height growth increments, $HT_t - HT_{t-1}$ divided by the time intervals (in years, to the month) between adjacent survey return dates. For each girl who was pre-menarche at baseline, we inspected her series of annualized growth increments and designated the largest her peak height growth velocity (PHV; inch/yr). Further details were provided earlier (17). The subgroup of

girls who were pre-menarche at baseline provided estimates of PHV for 34 BBD cases and 3848 non-cases.

Age at Menarche—Our surveys annually asked the girls "Have you started having menstrual periods?" and "If yes, age when periods began".

Family History—Our participants' mothers provided information regarding their own diagnoses of biopsy-confirmed BBD (to year 2005) and breast cancer (to 2009), and breast cancer in their mothers and sisters (to 2005). Their mothers and sisters are the maternal grandmothers and aunts of our participants.

Other Variables—At baseline, participants reported their race/ethnic group by marking all (of six) options that applied to them. Most females in this cohort are white/non-Hispanic (95%), as are all but three of the 67 BBD cases. We computed all ages (to the month) from dates of questionnaire return and birth.

Statistical Analyses

We estimated the prevalence of family history of breast cancer and maternal BBD for our GUTS participants. The prevalence of biopsy-confirmed BBD in our participants was estimated as well. Because we did not have information regarding when GUTS BBD cases were diagnosed, the outcome for analyses was prevalent BBD in logistic regression models. These models were estimated using SAS (28), which provided odds ratios (OR) and 95% confidence intervals (CI) for each risk factor, and the Hosmer-Lemeshow test of goodness of model fit. We used exact logistic regression whenever the numbers of BBD cases, in stratified analyses, were fewer than 10. Because age was related to each female's chance of being diagnosed with BBD during follow-up, we adjusted all models for exact age (to the month) at baseline; earlier work supported this particular age-adjustment (17). Our first series of models investigated how family history impacts risk for BBD. Subsequent models tested hypotheses, among girls with a family history, that childhood and adolescent body fatness, peak height growth velocity (PHV), age at menarche, young adult (at 18yrs or older) BMI and height, and adolescent alcohol intake are associated with BBD risk.

RESULTS

Prevalence of Family History; Selection Bias

Seventy-seven percent of females in the baseline (1996) GUTS cohort returned the 2005 and/or 2007 surveys that contained our questions regarding BBD. Of the original baseline cohort, 3.83% had a mother with breast cancer; there was little difference in this percent between females included and absent (due to no 2005 or 2007 survey) from the present analyses (3.85% versus 3.75%; p=.86). Over 18% of the girls' mothers had a biopsy-confirmed BBD, again with little difference between those present versus absent from these analyses (18.7% versus 18.6%; p=.81). Maternal grandmothers with breast cancer were similarly represented (11.0% versus 10.8%, p=.73), as were girls with an aunt (mother's sister) with breast cancer (3.5% versus 3.0%, p=.26). Our earlier papers (13,17) assessed selection bias in the other risk factors investigated here; included girls tended to be slightly younger at baseline (by 6 weeks), and reported slightly less alcohol consumption (by .01 drink/week) (both p<.05), but they were similar at baseline (to those absent from these analyses) in age-adjusted BMI, height, menarche status, and total energy intake.

Impact of Family History on BBD Prevalence

The prevalence of BBD ranged from 0.75% for girls with no family history (no maternal BBD and no family history of breast cancer) to 1.9% and 2.5% for girls whose mothers or

aunts had breast cancer (Table 1). Means, within family history groups, of the factors to be investigated are presented in Table 1. Age-adjusted logistic models (Table 2) indicated that maternal BBD may increase her daughter's risk of BBD by over 50% (marginally significant, p=.096), while breast cancer in the mother or aunt doubled her risk of BBD (OR=2.34, p=.01), but breast cancer in the grandmother did not increase the granddaughter's risk (OR=1.41, p=.32). It was unexpected that an aunt with BC (OR=2.71, 95%CI: 1.16–6.34) appeared a stronger risk factor than a mother with BC (OR=2.07, CI: 0.83–5.20), but this difference was not statistically significant. The mean age at breast cancer diagnosis among these mothers was 47.6yr, while mean diagnosis age among the aunts was 47.4yr, and 60.9yr among the grandmothers; thus, BBD cases in our GUTS females (in their 20's) appear to be more strongly linked to breast cancer cases diagnosed at younger ages in their mothers and aunts, than to cases in their grandmothers, many of them diagnosed at much older ages. Relative to girls with no family history of breast cancer or maternal BBD, girls whose mother or aunt were diagnosed with breast cancer before age 50yr were at greater BBD risk (OR=2.88, p=.01) than girls whose mother or aunt were diagnosed at age 50 or later (OR=2.67, p=.11). Similarly, girls whose mother, aunt or grandmother had BC diagnosed before age 50yr again had greater BBD risk (OR=2.35, p=.03) than girls whose family member was diagnosed later (OR=2.06, p=.04). Girls with a family history of breast cancer (mother, aunt, or grandmother) were at significantly increased risk for BBD (OR=1.92, CI: 1.12–3.27), as were those with a family history of breast cancer or maternal BBD (OR=1.97, CI: 1.22–3.20). Further fitting a dose-response model (number of family members, counting multiple aunts, with breast cancer) showed that girls with one family member may be at increased risk for BBD (OR=1.74, p=.058), while those with two or more family members were at considerably greater risk (OR=4.26, p=.02).

Risk Factors for BBD, in Girls with Family History of Breast Cancer

Due to our small number of biopsy-confirmed BBD cases in GUTS females, we recommend cautious interpretation of findings from logistic models fit to subgroups defined by family history (Table 3). The effect of each risk factor was estimated from a separate age-adjusted model. Girls whose mothers had breast cancer may be at even greater risk if they regularly drink alcohol (OR=4.03 for those who consume seven drinks per week compared to nondrinkers, CI: 0.65–16.71; p=.11), and similarly for girls whose aunt had breast cancer (OR=3.60 for those consuming 7 drinks/week, CI: 0.81–16.10; p=.09). (For interpreting our results, "seven drinks per week" is equivalent to "per daily drink".) The combined (mother or aunt) risk (OR=3.80, p=.02) is shown Table 3, along with the alcohol risk for girls whose grandmother had BC (OR=2.29, CI: 1.06–4.95 p=.04). The small numbers of GUTS girls with BBD (5 with Mom BC, 6 with Aunt BC, and 10 with Grandmother BC) represent 19 different girls diagnosed with BBD, so there is little overlap in cases. It is therefore impressive that alcohol has a large odds radio in separate analyses of the three groups (mother OR=4.03, aunt OR=3.60, grandmother OR=2.29). For 1157 girls with any family history of BC (mother, aunt, grandmother), the BBD risk for those who consume seven alcoholic drinks per week, compared to nondrinkers, is OR=2.28 (p=.01)(Table 3). Among girls whose mothers had BC, the only other factor that appeared to increase risk was more rapid peak adolescent height growth (PHV OR=2.03/(inch/yr), CI: 0.90–4.55, p=.08); for girls whose aunt had BC, the estimated risk associated with PHV was OR=1.90/(inch/yr), CI: 0.84–4.03, p=0.11). For mothers and aunts combined, the estimated effect was OR=1.82/(inch/yr) (p=.05)(Table 3), but this effect was entirely absent for girls whose grandmothers had BC (OR=.71, p=.51)(Table 3). None of the other factors appeared important for girls with a family history of breast cancer.

Risk Factors for BBD, in Girls with Maternal BBD

Among 1264 girls whose mothers had BBD, 18 of these girls were themselves biopsy-confirmed BBD cases (Table 3). Girls with maternal BBD were at higher risk for BBD the more alcohol they consumed (OR=1.96 for seven drinks per week, p=.02). None of the other factors were important.

Combined Risks for BBD: Alcohol

Above we found that girls with a family history of breast cancer were at increased risk for BBD the more alcohol they consumed (OR=2.28/(daily drink), p=.01; Table 3). And we similarly found that girls with maternal BBD were at increased risk if they drink (OR=1.96/(daily drink), p=.02; Table 3). A further analysis (not shown) finds the combined risk of OR=2.02/(daily drink) (p=.004) for girls with either maternal BBD or a family history of breast cancer, while the estimated risk for girls with both maternal BBD and familial breast cancer is OR=2.36/(daily drink) (p=.08). For girls with maternal BBD but no FH of breast cancer, the estimated risk associated with alcohol is OR=1.75/(daily drink) (p=.12), and for girls with any family history of breast cancer but not maternal BBD the estimate is OR=2.24/(daily drink) (p=.066). Finally, looking at the combined risk associated with family history and alcohol, girls with any family history of disease (breast cancer or maternal BBD) and who are in the highest quartile of alcohol consumption for their age (≥1 drink/wk for age 16yr, 2 drinks/wk for 18yr, 3 drinks/wk for 19yr) have significantly greater BBD risk (OR=2.27, p=.03) relative to girls with no family history who do not drink any alcohol.

Risk Factors for BBD, in Girls with No Family History of BC and No Maternal BBD

We now briefly look at girls with no family history of breast cancer and no maternal BBD (n=4678); 35 of these girls were BBD cases (Table 3, far right column). The important risk factors for these participants differed from those with a family history of disease. Elevated BBD risk was marginally associated with adult height (OR=1.11/inch, p=.08), childhood BMI (OR=0.88/(kg/m^2), p=.055), young adult BMI (OR=.91/(kg/m^2), p=.06), and significantly with adolescent waist circumference (OR=.86/inch, p=.02). The other factors were null.

DISCUSSION

Women who have been diagnosed with breast cancer, or whose mother or sister have had the disease, may ask how their daughters might reduce their cancer risk. Our analyses of young women consistently suggested, regardless of the exact nature of family history (breast cancer in her mother, aunt, or grandmother, or biopsy-confirmed BBD in her mother), that avoiding alcohol intake during adolescence may reduce her risk of BBD as a young woman, which likely reflects reduced risk of breast cancer (9). This is consistent with retrospective studies that linked adolescent alcohol intake to breast cancer (18, 29). Our family history subgroups had little overlap and thus provided fairly independent analyses, yet each produced a similar conclusion regarding alcohol consumption by adolescent females. Other factors that often are associated with breast cancer risk (less adiposity from childhood to young adulthood, and greater adult height) were associated with BBD only among girls with no family history of BC or maternal BBD. Age at menarche was null for all family history groups; this was not unexpected since women with BBD are not protected against breast cancer by later menarche (30). Our finding that more rapid peak height growth (PHV) may increase BBD risk among girls whose mother or aunt had breast cancer is consistent with a heritable component in which deficient DNA repair genes exert influence prior to BBD (12). Earlier research suggested that more rapid height growth is associated with elevated risk of breast cancer (18–20). However, we have less confidence in our finding on rapid height

growth and BBD because the estimated effects were less consistent across family history subgroups, particularly for grandmothers with BC.

Our finding that females with a family history of BC are more likely to themselves be diagnosed with BBD (OR=1.92, 95%CI: 1.12–3.27) is consistent with an earlier study in which women aged 25–29yrs with a family history of BC were at comparable elevated risk (RR=1.96, 95%CI: 1.55–2.47)(11). One possible explanation for BC in aunts providing slightly higher risk than BC in moms (Table 2), though not statistically significant and probably due to chance, is that if an aunt had breast cancer and did not survive, that aunt's cancer was reported to us by the participant's mother, but if the mother had breast cancer and did not survive to 1996, when our study was initiated by contacting the mothers, then that daughter never became part of the GUTS cohort. It was similarly unexpected that grandmother's BC was not a stronger risk factor, but many BC cases in grandmothers occurred at older ages, whereas BBD in GUTS girls (now in their 20's) may be a risk factor for breast cancer at younger ages (as in their moms and aunts). This is consistent with a study (11) in which women with a first degree relative with breast cancer were at even greater risk for BBD if the relative was diagnosed before age 50 (RR=1.81) than after age 50 (RR=1.57), though our grandmothers were second degree relatives. That study further demonstrated that adult women with a family history of breast cancer are at especially increased risk for the high-risk types of BBD (proliferative changes with atypia) that are more strongly associated with breast cancer.

Our analyses support the concept that risk factors for breast cancer may differ between women with a family history of breast cancer and women without a family history (7). Our finding that adult height appeared associated with BBD risk only among girls without a family history (Table 3) is consistent with data from a Swedish cohort (women aged 50–74yr), in which height was related to increased breast cancer risk in subjects without a family history, but not in subjects with a family history (1). And a study of young breast cancer patients (under 50yr of age), whose controls were their own twin sisters, found that childhood height and weight were associated with breast cancer risk only among those without a family history (8), again consistent with our findings.

The longitudinal design is a major strength of this investigation, as alcoholic beverage intakes, height, weight, and menarche data were collected years prior to the collection of BBD data in this large cohort of young females from all over the US. We controlled for baseline age in all models, but some residual and unmeasured confounding may remain; multivariate analyses in our earlier publications (13,17) provided odds ratios that were barely different from the age-adjusted estimates (except for young adult BMI, whose effect was greatly diminished with childhood BMI in the model).

A major limitation is the small number of GUTS BBD cases within family history subgroups, particularly girls having mothers with BC and girls having aunts with BC. Logistic model estimates obtained from data including fewer than 10 outcome events (BBD cases) should be interpreted with great caution, as there may be a 10% bias away from the null in the estimated effect of any continuous risk factor (31). But the general consistency of our estimated alcohol effects, across family history subgroups, enhances confidence in those conclusions. Another limitation was the necessity to collect data by self-report on (paper and online) questionnaires, but with our large, geographically dispersed cohort, alternatives were not feasible. We cited a validation study demonstrating that young women who reported BBD confirmed by biopsy were very reliable (23). Another issue regards detection bias, for girls with a family history of disease are much more likely to seek medical attention for a lump and their physicians more likely to perform a biopsy (32). This may result in more valid outcome data for girls with (than without) a family history, which is not a major

problem for this particular analysis since our primary purpose is to study those with a family history. But among GUTS girls without any known family history, this may indicate under-diagnosis of BBD. Thus, adolescent alcohol consumption may still be an important BBD risk factor for those without any family history, but we may have under-estimated the alcohol effect because of the larger numbers of girls whose BBD is un-diagnosed. However, our findings regarding the other factors (height and adiposity) among those with no family history are generally consistent with published risk factors for breast cancer. Reporting errors in childhood height, weight, menarche, and alcohol consumption are likely non-differential with respect to BBD status later on, resulting in underestimates of true associations.

Another possible limitation is that, although this was intended to be a cohort of biological offspring (we sent recruitment letters only to women with one or more childbirths during the relevant time period), a small number of adopted children apparently were entered into the cohort by the mothers along with their biological children. We already excluded entirely (from all analyses in this paper) those daughters who the mothers reported (after baseline) as adopted. However, we further conducted sensitivity analyses in which we excluded an additional small number of girls who we suspect may be adopted (for example, if biological father's height and maternal weight gain during pregnancy was not reported by the mother), and replicating our analyses produced odds ratios nearly identical to those reported here.

Although our cohort is not representative of US females, the comparison of risks within our cohort should still be valid and generalizable (33). Because our participants are daughters of nurses, this reduces confounding by socioeconomic and other unmeasured factors, while enhancing the accuracy of the information provided. But the racial/ethnic makeup of our cohort (95% white/non-Hispanic) hinders generalization to other races and ethnicities. Continued follow-up of this cohort will increase both the numbers of young women diagnosed with BBD and numbers with a family history of disease; future work should evaluate risk factors separately for females with, and without, a family history.

In conclusion, alcohol consumption by adult women is one of few modifiable factors known to increase breast cancer risk (14–16), and our work provides evidence that girls with a family history may reduce their own risk by avoiding alcohol intake during adolescence.

Acknowledgments

Funding Sources: Grant DK46834 (PI: Colditz) from the National Institutes of Health (Bethesda, MD) funded the initiation of the cohort and the collection/management of the data during years of followup. The Breast Cancer Research foundation (NYC, NY) funded the design, conduct and analysis of this specific manuscript (PI: Colditz). Neither sponsor was involved in the preparation, review, or approval of the manuscript. Dr. Frazier was supported by an award from the American Institute for Cancer Research. Dr. Colditz was supported, in part, by an American Cancer Society Clinical Research Professorship.

Professor Walter Willett provided valuable input to this work. We sincerely appreciate the ongoing support of the GUTS participants.

References

1. Magnusson C, Colditz G, Rosner B, Bergstrom R, Persson I. Association of family history and other risk factors with breast cancer risk (Sweden). Cancer Causes Control. 1998; 9:259–67. [PubMed: 9684706]
2. Welsh ML, Buist DS, Aiello Bowles EJ, Anderson ML, Elmore JG, Li CI. Popultion-based estimates of the relation between breast cancer risk, tumor subtype, and family history. Breast Cancer Res Treat. 2009; 114:549–58. [PubMed: 18437558]

3. Phipps AL, Buist DS, Malone KE, Barlow WE, Porter PL, Kerlikowske K, Li CL. Family history of breast cancer in first-degree relatives and triple-negative breast cancer risk. Breast Cancer Res Treat. 2010 Sep 3. [Epub ahead of print].
4. Wei EK, Wolin KY, Colditz GA. Time course of risk factors in cancer etiology and progression. J Clin Oncol. 2010; 28:4052–7. [PubMed: 20644083]
5. Brandt A, Bermejo J, Sundquist J, Hemminki K. Age of onset in familial breast cancer as background data for medical surveillance. Br J Cancer. 2010; 102:42–7. [PubMed: 19904271]
6. Colditz GA, Willett WC, Hunter DJ, Stampfer MJ, Manson JE, Hennekens CH, Rosner BA. Family history, age and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA. 1993; 270:338–43. [PubMed: 8123079]
7. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. (NHS). J Natl Cancer Inst. 1996; 88:365–71. [PubMed: 8609646]
8. Swerdlow AJ, De Stavola BL, Floderus B, Holm NV, Kaprio J, Verkasalo PK, Mack T. Risk factors for breast cancer at young ages in twins: an international population-based study. J Natl Cancer Inst. 2002; 94:1238–6. [PubMed: 12189227]
9. Schnitt, SJ.; Connolly, JL. Pathology of benign breast disorders. In: Harris, JR.; Lippman, ME.; Morrow, M.; Osborne, CK., editors. Diseases of the Breast. 3. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 77-99.
10. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed BBD. Cancer. 2006; 107:1240–7. [PubMed: 16902983]
11. Webb P, Byrne C, Schnitt S, Connolly J, Jacobs T, Peiro G, Willett W, Colditz GA. Family history of breast cancer, age and benign breast disease. Int J Cancer. 2002; 100:375–8. [PubMed: 12115556]
12. Jorgensen TJ, Helzisouer KJ, Clipp SC, Bolton JH, Crum RM, Visvanathan K. DNA repair gene variants associated with benign breast disease in high cancer risk women. Cancer Epidemiol Biomarkers Prev. 2009; 18:346–50. [PubMed: 19124519]
13. Berkey CS, Willett WC, Frazier L, Rosner B, Tamimi R, Rockett H, Colditz G. Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics. 2010; 125:e1081–7. Epub 2010 Apr 12. [PubMed: 20385629]
14. Chen WY, Colditz GA, Rosner B, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Ann Intern Med. 2002; 137:798–804. [PubMed: 12435216]
15. Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol. 2007; 165:667–76. [PubMed: 17204515]
16. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA. 1988; 260:652–6. [PubMed: 3392790]
17. Berkey CS, Willett W, Frazier, Rosner, Tamimi, Colditz GA. Prospective Study of Growth and Development in Older Girls and Risk of Benign Breast Disease in Young Women. Cancer. 2011; 117:1612–20. [PubMed: 21328325]
18. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer. 1999; 85:2400–9. [PubMed: 10357411]
19. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. NEJM. 2004; 351:1619–26. [PubMed: 15483280]
20. De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME. Childhood growth and breast cancer. Am J Epidemiol. 2004; 159:671–682. [PubMed: 15033645]
21. Colditz GA, Hankinson SE. The Nurses' Health Study: Lifestyle and health among women. Nat Rev Cancer. 2005; 5:388–96. [PubMed: 15864280]
22. Berkey CS, Rockett HRH, Gillman MW, Colditz GA. One-year changes in activity and in inactivity among 10- to 15-year old boys and girls. Relationship to change in BMI. Pediatrics. 2003; 111:836–843. [PubMed: 12671121]
23. Su X, Colditz GA, Willett WC, et al. Genetic variation and circulating levels of IGF-I and IGFBP-3 in relation to risk of proliferative benign breast disease. International Journal of Cancer. 2010; 126:180–90.

24. Neinstein LS. Breast disease in adolescents and young women. Pediatr Clin North Am. 1999; 46:607–29. [PubMed: 10384810]
25. Brener N, Billy J, Grady W. Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature. J Adolesc Health. 2003; 33:436–457. [PubMed: 14642706]
26. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiology. 2000; 152:446–52.
27. Berkey CS, Colditz GA, Rockett HRH, Frazier AL, Willett WC. Dairy consumption and female height growth: prospective cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2009; 18:1881–7.
28. SAS Institute Inc. Proc Logist. Cary, NC: SAS Institute Inc; 1997. SAS/STAT Software: Changes and Enhancements Through Release 6.12.
29. Garland M, Hunter D, Colditz G, et al. Alcohol consumption in relation to breast cancer risk in a cohort of United States Women 25–42 Years of Age. Cancer Epidemiol Biomarkers Prev. 1999; 8:1017–21. [PubMed: 10566558]
30. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–964. [PubMed: 11092437]
31. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007; 165:710–718. [PubMed: 17182981]
32. Elmore JG, Wells CK, Howard DH, Feinstein AR. The impact of clinical history on mammographic interpretations. JAMA. 1997; 277:49–52. [PubMed: 8980210]
33. Willett WC, Blot WJ, Colditz GA, Folsom AR, Henderson BE, Stampfer MJ. Merging and emerging cohorts: Not worth the wait. Nature. 2007; 445:257–258. [PubMed: 17230171]

Table 1

Characteristics of GUTS girls by family history of breast cancer or maternal BBD (GUTS girls: N=67 biopsy-confirmed BBD cases, 6741 non-cases).

Family History Disease Group:					
	FamHist None*	**Mother BBD**	**Mother BC**	**Aunt BC**	**Grandmother BC**
GUTS girls N=	4678	1264	260	237	749
GUTS BBD cases N= (biopsy-confirmed)	35	18	5	6	10
Percent BBD cases(%)	0.75	1.42	1.92	2.53	1.34
Risk Factor Means:					
Baseline age (yrs)	12.0	12.1	12.0	12.1	12.1
Adoles Alcohol (drinks/day)	0.2	0.2	0.2	0.2	0.2
PHV (inch/yr)	3.4	3.3	3.3	3.6	3.3
Menarche age (yr)	12.8	12.9	12.8	12.9	12.9
Adult height (in)	65.4	65.3	65.3	65.2	65.4
Childhood BMI (kg/m^2)	18.2	17.9	18.4	18.1	18.1
BMI change (kg/m^2)	4.5	4.5	4.5	4.2	4.3
Young Adult BMI (kg/m^2)	23.7	23.5	23.9	23.3	23.5
Adoles Waist circumf (inch)	29.5	29.2	29.5	29.3	29.5

* "FamHist None" group omits girls with either maternal BBD or family history of breast cancer.

Table 2

Risk of biopsy-confirmed BBD in GUTS girls (N=67 cases, 6741 non-cases) associated with family history of breast cancer or maternal BBD. Odds ratios (OR) obtained from logistic regression models; all models include baseline ages of GUTS girls.

	UNIVARIATE		**MULTIVARIATE (family BC, mother BBD)**		**MULTIVARIATE (family BC)**	
	OR	**p-value**	**OR**	**p-value**	**OR**	**pvalue**
Mother BC	2.07	.12	1.85	.195	1.91	.17
Aunt BC (Mother's sister)	2.71	.022	2.52	.03	2.57	.03
Maternal Grandmother BC	1.41	.324	1.33	.41	1.36	.38
Mother BBD	1.59	.095	1.52	.13		
******Mother and Aunt breast cancer cases combined*****						
Mother and/or Aunt	2.34	.01	2.24	.02	2.32	.015

Cancer. Author manuscript; available in PMC 2013 June 01.

Table 3

Risk of biopsy-confirmed BBD in young females with family history of breast cancer (BC), maternal BBD, and in females with no family history. Odds ratios were obtained from age-adjusted logistic regression models.

Family History	**Breast Cancer in Affected Family Member**			**BBD**	**None**
	Mother or Aunt	**Grandmother**	**Any Family Member (Mother, Aunt, Grandm)**	**BBD in Mother**	**No Family History**
GUTS girls N=	477	749	1157	1264	4678
GUTS BBD cases N=	10	10	19	18	35
Risk Factor OR (p-value):					
Adoles Alcohol (daily drink)	3.80 (.02)	2.29 (.04)	2.28 (.01)	1.96 (.02)	1.22(.57)
PHV (inch/yr)	1.82 (.05)	0.71 (.51)	1.21 (.49)	1.31 (.44)	1.08 (.70)
Menarche age (yr)	1.21 (.47)	1.08 (.77)	1.05 (.78)	1.00 (.99)	1.12 (.42)
Young adult height (inch)	0.95 (.67)	0.93 (.54)	0.96 (.64)	1.07 (.44)	1.11(.08)
Childhood BMI (kg/m^2)	1.00 (.97)	0.83 (.16)	0.93 (.37)	0.99 (.90)	0.88 (.055)
BMI change (kg/m^2)	1.03 (.72)	1.06 (.59)	1.04 (.58)	1.05 (.44)	0.94 (.33)
Young Adult BMI (kg/m^2)	1.02 (.81)	0.94 (.51)	0.99 (.80)	1.02 (.63)	0.91 (.06)
Adoles Waist circumfer (in)	0.92 (.51)	0.90 (.37)	0.91 (.27)	1.08 (.30)	0.86 (.02)

Note: BMI change is from baseline to young adulthood; Childhood BMI and BMI change appear together in models.